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## REMARKS

### The Invention.

The present invention provides a method of generating a DNA library of variant protein of interest. The construction of the library employs a probability matrix for a reference sequence, and a constraint vector for which is applied to the probability matrix to produce a substitution scheme. The substitution scheme is then used to generate a library comprising substitutions in the nucleotide sequence that results in a change in the amino acid(s) recommended by the substitution scheme. The library members, or host cells comprising and/or expressing them, can be screened for desired changes in a property of interest in the polypeptides in the library.

### Status of the Application.

Claims 1-6, 11, 15-23, 25-29 and 31 are pending in the application. Claim 1 has been amended to correct a grammatical error. Applicants assert new matter has not been introduced by the amendment.

### 35 U.S.C. §102

A reference that merely contains substantially the same elements or only broadly teaches the invention is insufficient to establish anticipation. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 756 F.2d 1556, 1560, 225 USPQ 253, 256 (Fed. Cir. 1985); *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 772, 218 USPQ 781, 789 (Fed. Cir. 1983).

### 35 U.S.C. §102(b).

Claims 1, 5, 6, 11, 15-23, 25-27 and 31 were rejected under 35 USC 102(b) as being anticipated by Hatfield *et al.* (US Patent 5,082,767). Specifically, the Examiner asserts that Hatfield *et al.* uses a probability matrix and a constraint vector to derive a recommended substitution scheme. The substitution scheme is then used, according to the Examiner, to "alter or construct genes for the purpose of expression in other organism" and that the Hatfield method uses a computer program. See pages 3 and 4. Therefore, the Examiner asserts that Hatfield *et al.* anticipates the present invention. Applicants respectfully traverse.

It is well-settled law that to anticipate a claim the prior art reference must contain each and every element within the four corners of the document. Thus, Applicants submit that there can be no anticipation unless all of the same elements of the invention are found within the four corners of

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a single reference. *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747, 3 USPQ2d 1766, 1767-68 (Fed. Cir. 1987). A reference that merely contains substantially the same elements or only broadly teaches the invention is insufficient to establish anticipation. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 756 F.2d 1556, 1560, 225 USPQ 253, 256 (Fed. Cir. 1985).

Applicants further submit that the Hatfield *et al.* reference fails to teach each and every element of the claimed invention. Specifically, Hatfield *et al.* does not describe the substitution of amino acid(s) in the protein of interest. The mere substitution of a nucleotide to enhance expression fails to teach the instant invention. There is no mention that the nucleotides should be altered to introduce an amino acid substitution into the protein of interest to effect a change in a characteristic of the protein of interest, e.g., specific activity. In contrast, the instant method can be used to introduce amino acid residues, i.e., substitutions, that are not contained in the parent reference sequence but that are still likely to preserve structure and function.

Given the strict standards for anticipation, it is readily apparent that there is no anticipation of the claimed invention in view of Hatfield *et al.* Withdrawal of the rejection is respectfully requested.

### **35 U.S.C. §103.**

Claims 1-6, 11, 15-28 and 31 were rejected under 35 USC 103(a) as being unpatentable over Hatfield *et al.* in view of Blattner *et al.* Applicants respectfully traverse.

Hatfield *et al.* was discussed above. Blattner *et al.* fails to cure the deficiencies of Hatfield *et al.* Neither reference teaches the mutation of the amino acid sequence of a protein of interest. Blattner *et al.* provides the nucleotide sequences for certain enumerated proteins but does not indicate that it would be beneficial or desirable to mutate them in order to alter their respective proteins amino acid sequence. Neither reference teaches or suggests the mutation of the amino acid sequence of a protein of interest. Therefore, neither of the references, whether alone or together, discloses the presently claimed invention and do not render obvious the claimed invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

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**CONCLUSION**

In light of the above amendments, as well as the remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7615.

Respectfully submitted,  
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